**PCT** WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 209/14, A61K 31/40

A1

(11) International Publication Number: WO 92/06955

(43) International Publication Date: 30 April 1992 (30.04.92)

(21) International Application Number: PCT/EP91/01940

(22) International Filing Date: 11 October 1991 (11.10.91)

(30) Priority data:
21768 A/90 17 October 1990 (17.10.90) IT

(71) Applicant *(for all designated States except US)*: PULITZER ITALIANA S.R.L. [IT/IT]; Via Tiburtina, 1004, I-00156 Rome (IT).

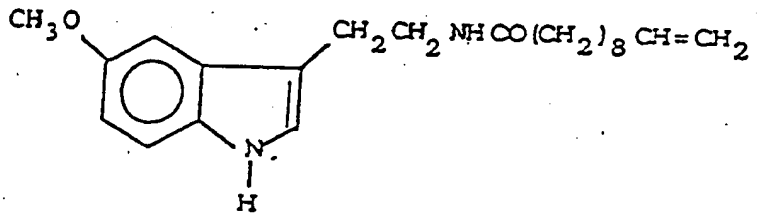
(72) Inventor; and
(75) Inventor/Applicant *(for US only)* : RAINOLDI, Angelo [IT/IT]; Via Tiburtina, 1004, I-00156 Rome (IT).

(74) Agent: MINOJA, Fabrizio; Studio Consulenza Brevettuale, Via Rossini, 8, I-20122 Milano (IT).

(81) Designated States: AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC, MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL (European patent), NO, PL, RO, SD, SE (European patent), SN (OAPI patent), SU+,TD (OAPI patent), TG (OAPI patent), US.

Published
*With international search report.*

(54) Title: MELATONIN DERIVATIVE HAVING THERAPEUTIC ACTIVITY IN DERMATOLOGY



(I)

(57) Abstract

5-Methoxy-N-(10-undecenoyl)-tryptamine, a process for the preparation thereof and the use thereof in dermatology are herein described.

+ See back of page

**+ DESIGNATIONS OF "SU"**

**Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.**

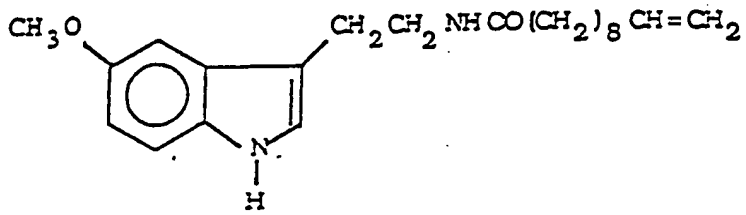
*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | |
|---|---|---|---|---|---|
| AT | Austria | ES | Spain | MG | Madagascar |
| AU | Australia | FI | Finland | ML | Mali |
| BB | Barbados | FR | France | MN | Mongolia |
| BE | Belgium | GA | Gabon | MR | Mauritania |
| BF | Burkina Faso | GB | United Kingdom | MW | Malawi |
| BG | Bulgaria | GN | Guinea | NL | Netherlands |
| BJ | Benin | GR | Greece | NO | Norway |
| BR | Brazil | HU | Hungary | PL | Poland |
| CA | Canada | IT | Italy | RO | Romania |
| CF | Central African Republic | JP | Japan | SD | Sudan |
| CG | Congo | KP | Democratic People's Republic of Korea | SE | Sweden |
| CH | Switzerland | | | SN | Senegal |
| CI | Côte d'Ivoire | KR | Republic of Korea | SU+ | Soviet Union |
| CM | Cameroon | LI | Liechtenstein | TD | Chad |
| CS | Czechoslovakia | LK | Sri Lanka | TG | Togo |
| DE | Germany | LU | Luxembourg | US | United States of America |
| DK | Denmark | MC | Monaco | | |

# MELATONIN DERIVATIVE HAVING THERAPEUTIC ACTIVITY IN DERMATOLOGY

The present invention relates to 5-methoxy-N-(10-undecenoyl)-tryptamine of formula



(I)

a process for the preparation thereof and pharmaceutical compositions containing it.

Melatonin is a hormon synthetised in epiphysis, retina and supposedly also in intestinal chromaffin cells. Melatonin biosynthesis follows a circadian rhythm and reaches its highest peak during night-hours.

The compound of the invention, which hereinafter will also be named PU 2049, is the condensation product from two pharmacologically active compounds: melatonin, which is already well known to be active in the treatment of psoriasis (as described in WO 87/00432) and 10-undecenoic acid, which has a remarkable antimicrobic, particularly antimycotic, activity.

It has now been found that PU 2049 has a better bioavailability in the case of topic administration.

The pharmacological tests evidenced that PU 2049 is particularly effective in the treatment of psoriasis and further has a good antimycotic effect and an interesting antiseborrhoic activity.

PU 2049 activity in the treatment of psoriasis was evidenced during a double blind test, wherein 20 patients suffering from psoriasis at their scalp (7 patients), at their elbows (5 patients), at their knees (4 patients), at their palms and/or their soles. The subjects were divided into two groups and treated with daily topic applications of a 0.3% PU 2049 hydroalcoholic solution (1st group) and melatonin (2nd group), which was used as reference compound. In both groups, the treatment was continued for 20 days running.

PU 2049 proved to have a higher therapeutic activity in reducing skin desquamation and erythema-papulosae lesions than that of melatonin. In fact, all the patients treated with PU 2049 showed an improvement, both during and after the therapy, which was significantly more marked than the one seen in the control group.

The antimycotic activity of the compound of the invention was tested on agar culture dishes, according to the method described by Bennett G.A. et al. (Arzneim. Forsch./Drug Res. 40, 210; 1990). PU 2049 antimycotic activity was particularly evident against some dermatophytes strains, like epidermophytes, trichophytes, microspores. In these tests, melatonin was inactive.

Further, PU 2049 was tested against hamster flank glands. These glands are rich in sebaceous cells, therefore they are a suitable mean to evaluate drug antiseborroic activity, as described by Lutsky B.N. et al. (J. Invest. Dermatol., 64, 412; 1975). According to

the present invention, a 0.3% PU 2049 hydroalcoholic solution or a melatonin hydroalcoholic solution were daily applied for 15 days running on flank skin of hamsters, weighing 90-100 g. A control group was treated with carrier only. At the end of the treatment, the glands of all the animals were withdrawn and weighed. The glands treated with PU 2049 showed a 45% weight decrease. Such an effect was significantly greater than the one obtained with melatonin.

It is therefore a further object of the present invention the use of PU 2049 as a therapeutic agent in formulations which can be prepared with conventional excipients and techniques, like those described in "Remington's Pharmaceutical Sciences Handbook" Mack Pub. Co., NY, USA.

The pharmaceutical compositions of the present invention contain from 1 to 500 mg PU 2049 and can be administered in one or more applications a day, according to symptom severity.

Examples of the above compositions are creams, ointments and oils, and every other formulation suitable for topic applications.

The compound of the invention can be prepared by reacting melatonin with 10-undecenoic acid or, more preferably, with a reactive derivative thereof (acid chloride, acid anhydride, imidazolide, and the like).

The use of the acid chloride comprises the presence of acid-binding agents (like pyridine, tertiary amines, alkali or alkaline-earth metal hydrogen carbonates) in inert solvents.

The following example further illustrates the

invention.

EXAMPLE

2.13 ml (0.01 mole) of 10-undecenoyl chloride were added to a solution (kept into darkness) containing 1.90 g (0.01 mole) of 5-methoxytryptamine (melatonin), dissolved in 50 ml of a benzene-pyridine (7/3) mixture. The reaction mixture was allowed to stand for 1 hour, while stirring at reaction temperature.

The solvent was evaporated under reduced pressure and the residue was taken up with benzene.

The organic phase was washed with 10% HCl, 5% NaOH and water. The organic layer was dried over sodium sulphate, the solvent was evaporated under reduced pressure and the residue was triturated in hexane/isopropyl ether, obtaining 1.9 g of PU 2049.

**NMR ($CDCl_3$):**

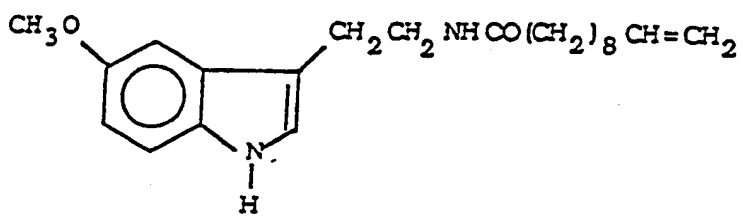
$\delta$ (p.p.m.) 1.2-1.7 (multiplet), 12H (alkyl $CH_2$); 1.9-2.3 (complex signal), 4H ($CH_2CH_2NH$, $CH_2CH=$); 2.95 (triplet, J-7Hz), 2H ($CH_2CO$); 3.5-3.7 (double triplet, triplet after deuteration), 2H ($CH_2NH$); 3.87 (singlet), 3H ($CH_3$); 4.8-5.1 (multiplet), 2H ($CH_2=$); 5.5-5.9 (complex signal), 2H (CH=, NHCO); 6.7-7.3 (multiplet) 4H (aromatic); 8.3 (broad singlet disappears after deuteration), 1H (NH).

**IR (Nujol):**

frequency ($cm^{-1}$) 3400, 3300 (NH); 1640 (CO).

CLAIMS

1. 5-Methoxy-N-(10-undecenoyl)-tryptamine of formula



(I)

2. A process for the preparation of the compound of claim 1 characterized by reacting melatonin with 10-undecenoic acid or with a reactive derivative thereof.

3. The compound of claim 1 as a therapeutic agent.

4. Pharmaceutical compositions containing the compound of claim 1 as the active ingredient, in admixture with suitable carriers.

5. The use of the compound of claim 1 for the preparation of a medicament useful for the treatment of psoriasis and mycotic infective diseases.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/01940

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 D 209/14, A 61 K 31/40

## II. FIELDS SEARCHED

Minimum Documentation Searched[7]

| Classification System | Classification Symbols |
|---|---|
| IPC5 | C 07 D; A 61 K |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in Fields Searched[8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category * | Citation of Document,[11] with indication, where appropriate, of the relevant passages[12] | Relevant to Claim No.[13] |
|---|---|---|
| A | WO, A3, 8700432 (CELLENA (CELL ENGINEERING) A.G.) 29 January 1987, see the whole document | 1-5 |
| A | US, A, 4746674 (W. PIERPAOLI ET AL.) 24 May 1988, see the whole document | 1-5 |

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 2nd January 1992 | 24 JAN 1992 |
| International Searching Authority: EUROPEAN PATENT OFFICE | Signature of Authorized Officer: MISS T. TAZELAAR |

Form PCT/ISA/210 (second sheet) (January 1985)

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.PCT/EP 91/01940

SA 52113

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 31/10/91
The European Patent office is in no way liable for theseparticulars which are merely given for the purpose of information.

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|
| WO-A3- 8700432 | 29/01/87 | AU-D- | 6142186 | 10/02/87 |
| | | EP-A- | 0229131 | 22/07/87 |
| US-A- 4746674 | 24/05/88 | AU-D- | 5626786 | 24/09/86 |
| | | EP-A- | 0214254 | 18/03/87 |
| | | WO-A- | 86/05093 | 12/09/86 |

For more details about this annex : see Official Journal of the European patent Office, No. 12/82

EPO FORM P0479